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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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RONALD I. EISENSTEIN
100 SUMMER STREET
NIXON PEABODY LLP
BOSTON, MA 02110

EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,709	CANTOR ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9-11* is/are allowed.

6)☒ Claim(s) *1-6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/24/2006;08/17/2006;04/10/2008;09/22/2008.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-6 and 8-11, in the reply filed on 01/22/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-6 and 8-11 are the only claims pending in the application.

Claim Interpretation

The claims are directed to detection of "rare" mutations. As there is no particular indication of how "rare" a mutation must be in order to be considered "rare", any mutation will be considered rare.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 5 the phrase "wherein a mixture of dNTP(s)/ddNTP(s)ddNTP(s) are used" is unclear. For purposes of examination over the prior art, this phrase will be construed as "wherein a mixture of dNTP(s) and/or ddNTP(s) are used".

With regard to claim 8, the phrase "and in the second reaction the detection primer is designed…". This phrase is ambiguous since the claim specifies that two detection primers are used. Hence, while the examiner will assume "the detection primer" in the second reaction refers to "the second detection primer" (as opposed to "the first detection primer"), the claim language should clearly state this.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Xue et al (US 2003/0017487 A1, cited on the IDS of 08/17/2006).

With regard to claim 1, Xue teaches a method of detecting nucleic acids with a rare mutation, wherein said rare mutation includes any change from the wildtype sequence including polymorphisms (see abstract for example). Xue's method comprises amplifying a nucleic acid molecule with primers flanking the rare mutation site (see figure 6 for example). Xue's method comprises purification of the amplified Product (see figure 6 for example), which would thus remove the excess dNTPs after the amplification reaction. Xue's method further comprises performing a primer extension reaction using a detection primer which is designed so that the 3' end of the detection primer is immediately adjacent to a nucleic acid which differentiates the wildtype from the mutant nucleic acid molecule (see figure 7 for example; note that

"primer 3" hybridizes to the amplified product so that its 3' end is immediately adjacent to the position of the SNP, i.e. the single nucleotide polymorphism that differentiates the wildtype and mutant sequence). Xue's primer extension reaction includes one dNTP (figure 7: dTTP) and one ddNTP (figure 7: ddGTP). Note that the dTTP corresponds to a nucleoside adjacent to the detection primer in the rare mutant nucleic acid molecule. Xue also teaches detecting the presence of the primer extension products to indicate the presence of the nucleic acid with the "rare" mutation (i.e. the SNP; see abstract for example: "The resultant elongation/termination reaction products are analyzed for the length of chain extension or the primer, or for the amount of label incorporation from a labeled form of the terminator nucleotide.").

With regard to claims 3 and 4, Xue used only one dNTP corresponding to a nucleoside differentiating the rare nucleic acid variant from the more common nucleotide variant (i.e. Xue used only the dNTP dTTP; see figure 7 for example).

With regard to claim 5, Xue teaches that the method "utilizes a null, single or double base extension of an oligonucleotide primer to identify a SNA" (paragraph [0001]). Note that several figures (e.g. figure 2, teach four separate reaction mixtures, each with a single dNTP and a single ddNTP for each of the four possible nucleotides present as the SNP. Since any of the four possible nucleotides of a SNP can be considered a "wildtype" whereas the other three possibilities can be considered "mutants", Xue teaches the limitations of claim 5. For example, when considering the "A" allele as the "wildtype", both the "A-Mix" and the "G-Mix" meet the limitations since

neither dATP or ddCTP of the A-Mix, nor dGTP or ddCTP of the G-Mix can be used for extension (i.e. incorporation opposite the "A" nucleotide at the SNP position:

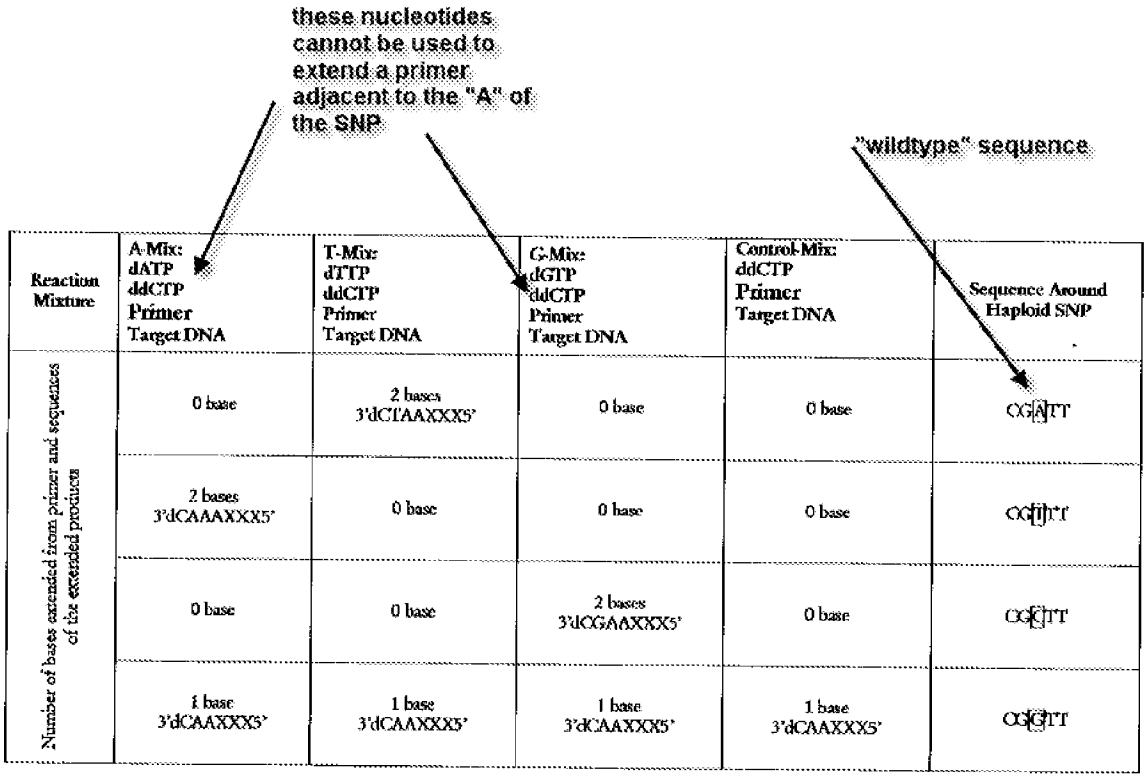

Fig. 2

With regard to claim 6, Xue teaches "comparing the predicted and experimentally determined quantity of label incorporation from a labeled ddNTP into the oligonucleotide primers" (paragraph [0034]). If one determines the quantity of label incorporated into a primer extension product, one also inherently measures the amount of the extension product itself.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Xue et al (US 2003/0017487 A1, cited on the IDS of 08/17/2006) in view of Landegren et al (Genome Research 8:769-76, 1998, cited on the IDS of 08/17/2006).

The teachings of Xue have been discussed. Xue does not teach sequencing by pyrosequencing.

Landegren teaches on page 773, section entitled "Minisequencing", that pyrosequencing can be used for detecting SNPs by primer extension. Pyrosequencing measures the consumption of dNTPs or ddNTPs based on the release of pyrophosphate from the nucleotide upon incorporation into the extended primer.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the method taught by Xue to detect the incorporation of nucleotides or dideoxynucleotides based on pyrosequencing as taught

by Landegren, since this was a known means in the art for detecting a SNP by primer extension.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Xue et al (US 2003/0017487 A1, cited on the IDS of 08/17/2006) in view of Fan et al (Genome Research 10:853-860, 2000).

The teachings of Xue have been discussed. Xue does not teach performing parallel primer extension reactions using two different detection primers, wherein the first detection primer is designed to amplify the sense strand so that the 3' end of the primer anneals immediately adjacent to the mutation (SNP) site in the sense strand and in the second reaction the detection primer is designed to amplify the antisense strand so that the 3' end of the primer anneals immediately adjacent to the mutation (SNP) site in the antisense strand.

Fan teaches designing SBE primers (single-base extension primers) for both the forward and reverse strands (i.e. the sense and antisense strands) when typing SNPs (see sentence spanning pages 854-855).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Xue to carry out parallel SNP typing by designing primers for both strands as taught by Fan in order to provide confirmation of the results, as the two parallel primer extension reactions should agree with one another. Furthermore, Fan teaches that in cases where poor amplification in the PCR or primer extension reactions (SBE reactions) fail or produce poor signals, the

typing of these SNPs may be rescued by using the opposite strand extension primer (page 855, column 2, first paragraph).

Allowable Subject Matter

The following is a statement of reasons for the indication of allowable subject matter: Claims 9-11 require amplifying a control nucleic acid having the same sequence as the rare mutation amplicon with the exception of one nucleic acid difference immediately adjacent to the mutation site. This feature is neither taught nor suggested in the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637